REMARKS

The specification has been amended to correct the caption of Fig. 6B so that it corresponds to Fig.6B as filed. In particular, Fig.6B as filed is an amino acid sequence of α2MR and the 80kDa portion of the sequence is not highlighted in bold. No new matter has been added by these amendments.

Claims 31, 71, and 76-93 are pending in the instant application. By this amendment, claims 31, 71, 79, and 87 have been amended and claim 83 has been canceled without prejudice to applicants' right to pursue the cancelled subject matter in this or related applications. In particular, claim 31 has been amended to indicate that "a purified compound" is "selected from the group consisting of an antibody, an alpha (2) macroglobulin fragment, an alpha (2) macroglobulin receptor fragment, and a heat shock protein fragment." Claim 71 has been amended to indicate that "a purified compound" is "selected from the group consisting of an antibody or an alpha (2) macroglobulin fragment and a heat shock protein fragment." Claims 31 and 71 have also been amended to delete the proviso at the end of the claims. Support for the amendments is found in Section 5.6.1.1.1 at page 51, lines 4 through page 53, line 17; page 53, line 32 through page 55, line 12; page 12, lines 13 to 20; and page 3, line 34 through page 4, line 15. Claims 79 and 87 have been amended to correct grammatical errors. No new matter has been added by these amendments.

Therefore, claims 31, 71, and 76-93 will be pending upon entry of the instant amendment in the instant application. Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

1. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN

Claims 31, 71, 76, and 80-91 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that the specification does not provide adequate written description support that is commensurate in scope to claims that read generically on any and all "compounds" and that there is only adequate support for a "compound" that is a purified antibody, but not for "antagonists", "small molecules", or "peptides." In particular, the Examiner contends that

> "there does not appear too be an adequate written description in the specification as-filed of the essential structural feature that

> provides the recited function of interfering with the interaction of a first heat shock protein with an α2MR."

In the interest of advancing prosecution and without acquiescing to the basis of Examiner's rejection, claims 31 and 71 have been amended to indicate that "a purified compound" is "selected from the groups consisting of an antibody, an alpha (2) macroglobulin fragment, an alpha (2) macroglobulin receptor fragment, and a heat shock protein fragment" and "selected from the group consisting of an antibody, an alpha (2) macroglobulin fragment, and a heat shock protein fragment," respectively. Claims 83 and 84 have been canceled without prejudice to Applicants' right to pursue the cancelled subject matter in this or related applications.

The criteria for determining sufficiency of written description set forth in Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description Requirement" ("the Guidelines") (published in the January 5, 2001 Federal Register at Volume 66, Number 4, pp. 1099-1111), specifies that an applicant may show that an invention is complete by "disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention." (*Id.* at page 1106, column 1, lines 22-33). According to the Guidelines, for each claimed genus, the test requires determination of whether there is sufficient description of

> " . . .a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus." *Id.* at page 1106, column 3, lines 12-29.

Where the specification discloses any relevant identifying characteristics, *i.e.*, physical, chemical and/or functional characteristics, sufficient to allow a skilled artisan to recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced.

On page 2, ¶ 4, the Office Action indicates that the specification provides sufficient support for an antibody, but does not provide adequate support for peptides that are capable of binding the α2MR. Applicants submit that the specification provides adequate written description support for the claimed α2M fragment, α2MR fragment, and HSP

fragment, as discussed in detail below.

The specification clearly describes types of compounds, including α2M fragments and HSP fragments, that can be used in the methods of the invention to modulate an immune response. For example, the specification describes, both structurally and functionally, α2M fragments that can be used in the methods of the invention. The specification teaches fragments that comprise at least 5 consecutive amino acids of the amino acid sequence of α2M, at page 10, lines 2-3 and page 51, lines 11-22. Functionally, the specification describes α2M sequences that comprise the α2MR binding domain (see page 37, lines. 16-19). The boundaries of the domain are described in the specification at page 13, lines 27-29, Fig. 7B and in the references provided at page 3, line 34 through page 4, line 7, including Salvesent *et al.*, 1992, FEBS lett. 313:198-202 and Holtet *et al.*, 1994, FEBS Lett. 344:242-246. Moreover, this domain is conserved and has been identified and defined in other α2MR ligands (see page 4, lines 8-13). Thus, a correlation between structure, *i.e.*, fragments of α2M having the α2MR binding domain, and function, *i.e.*, α2MR binding, is adequately described in the specification.

The use of HSP fragments in the methods of the invention is also described throughout the specification, in particular, at page 10, lines 4-6; page 29, line 30 through page 30, line 3; page 41, lines 4-27; and page 55, lines 14-17. HSP fragments that are useful in the methods of the invention include fragments that bind an α2MR (see page 55, lines 16 and 17). Structurally, the sequences of various HSPs are described in the specification at page 15, lines 14-30 where citations and Genbank references are provided for exemplary HSPs.

The use of α2MR fragments of at least 5 consecutive amino acids of the sequence is taught in the specification to modulate an immune response (see page 10, lines 1-2; and page 54, lines 7-27). The specification teaches that the extracellular domain of the α2MR binds to ligands such as HSPs (see page 37, lines 14-16). The specification describes α2MR fragments both structurally and functionally. The specification also describes the functional domains of the α2MR at page 13, line 36 through page 14, line 5, Fig. 8A, and Herz *et al.*, 1988, EMBO J. 7:4119-4127 and Horn *et al.*, 1997, J. Biol. Chem. 272:13608-13613 referenced therein (IDS reference Nos: AZ and BD, previously submitted).

The specification also describes an example of an α2MR ligand-binding peptide as an 80 kDa ligand-binding α2MR fragment described in Example 6 (see page 17, lines 19-22 and page 73, lines 13-19). This 80kDa fragment is shown highlighted in bold in Fig.8B (see Fig. 8B and page 14, lines 2-3). In view of this example and the structural and functional descriptions of α2MR fragments, the specification provides adequate written

description support for exemplary α2MR fragments.

Antibodies, α2MR fragments, HSP fragments, and α2M fragments that provide the recited function of interfering with the interaction of a first heat shock protein with an α2MR are adequately described in the specification sufficient to meet the written description requirement. Thus, it would be apparent to one skilled in the art, at the time the application was filed, that the applicants had possession of methods for modulating an immune response using a purified antibody, an α2M fragment, an HSP fragment, or an α2MR fragment that interferes with the interaction of a heat shock protein and the α2MR or binds the α2MR.

In view of the forgoing arguments and amendments, applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

2. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 31, 71, 76, and 77-93 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking an enabling disclosure. The Examiner contends that one skilled in the art would not be able to practice the invention commensurate in scope to the claims because the outcome of the *in vivo* administration of purified compounds for the treatment of diseases is unpredictable and would require undue experimentation on behalf of one skilled in the art. The Examiner also contends that treatment of cancer is unpredictable, including extrapolating from *in vitro* to *in vivo* protocols.

According to case law, undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

Furthermore, Applicants emphasize that 35 U.S.C. § 112 does not require *in vivo* testing of the methods encompassed by the claims. In particular, the Federal Circuit has deemed results of *in vitro* tests sufficient as long as they are reasonably correlated with a pharmacologically useful *in vivo* response. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39

U.S.P.Q.2d 1895, 1899 (Fed. Cir. 1996). For example in *Fujikawa*, the court found that the claimed cholesterol inhibiting compound had utility even in the face of testimony and research articles indicating that inhibition of cholesterol biosynthesis *in vitro* did not always correspond to the inhibition of cholesterol anabolism *in vivo*. *Fujikawa*, 93 F.3d at 1566, 39 U.S.P.Q.2d at 1900.

In the present instance, the Examiner contends that the *in vitro* data disclosed in the specification cannot be extrapolated to *in vivo* protocols for the treatment of cancer because of the unpredictability of the art of cancer therapy. Applicants point out that the claimed methods of the rejected claims are methods for inhibiting or modulating an immune response, and their utility is supported by cell-based assays for immune response. Applicants submit that such assays correlate well with inhibiting or modulating an immune response *in vivo* and that all of the compounds used in the methods of the invention are enabled for modulating an immune response, for the reasons discussed in detail below.

As discussed above, claims 31 and 71 have been amended in response to the written description rejection to indicate that "a purified compound" is "selected from the group consisting of an antibody, an alpha (2) macroglobulin fragment, an alpha (2) macroglobulin receptor fragment, and a heat shock protein fragment" or is "selected from the group consisting of an antibody, an alpha (2) macroglobulin fragment, and a heat shock protein fragment," respectively. Each of the types of compounds recited in the amended claims is fully enabled by the specification. The specification teaches that compounds of these types can be used to interfere with the interaction between the α2MR and an HSP.

With respect to antibodies, the specification teaches how to make antibodies that can be used in the methods of the invention in Section 5.3.1 at page 23-26. The specification also provides an example where it is shown that rabbit antiserum containing antibodies against the 80kDa fragment of the α2MR inhibited re-presentation of a gp96-chaperoned antigenic peptide in an *in vitro* model using cells involved in *in vivo* re-presentation of peptides (see Example 6 page 72, line 29 through page 73, line 7). These results indicate that anti-α2MR antibodies interfere with the interaction of a heat shock protein and the α2MR. The interference of the interaction in turn inhibits the presentation of the heat shock protein-chaperoned peptide in the cells. Blocking presentation of a peptide *in vivo* would in turn interfere with an immune response. The *in vitro* example of antigen re-presentation disclosed in the specification is a live cell-based assay that utilizes cell types, *i.e.*, macrophage cells, involved in immune responses *in vivo*. Applicants assert that it would not be unreasonable to extrapolate these *in vitro* cell culture assay results to *in vivo* systems

because the same essential mechanism of peptide presentation is maintained in cells *in vivo*.

In support of this assertion, applicants submit Binder and Srivastava (2004, Proc. Natl. Acad. Sci. U.S.A. 101:6128-6133, hereafter "Binder and Srivastava," submitted herewith as Information Disclosure Statement "IDS" reference No. C02) which demonstrates that inhibition of re-presentation of gp96-ova20 peptides *in vitro* in the presence of α2M also was observed *in vivo* in the presence of an α2M (see caption of Fig. 2A at page 6130 and caption of Fig. 3B at page 6131). Thus, comparable results were obtained in both *in vitro* and *in vivo* re-presentation assays using α2M. Results using the same assays also demonstrated that an anti-α2MR (anti-CD91) antibody behaves similarly *in vivo* (see Fig. 3B at page 6131). Thus, it is possible to successfully extrapolate the type of *in vitro* cell culture results disclosed in the specification to *in vivo* systems.

Accordingly, Applicants submit that following the teachings of the specification, antibodies can be used *in vivo* to successfully interfere with the interaction of a. HSP and an α2MR and thereby modulate an immune response *in vivo*. For example, the specification describes the inhibition of *in vitro* re-presentation of gp-96 chaperoned peptides by immune sera to the 80 kDa fragment of the α2MR (page 72, line 29 through page 73, line 12). Binder and Srivastava extended upon this observation and demonstrated that, in accordance with the teachings of the specification, the use of anti-α2MR antibodies have comparable results in an *in vivo* model of antigen representation and functionally correlate to an *in vivo* animal model of tumor rejection. Anti-α2MR antibodies were shown to successfully inhibit re-presentation of gp96-chaperoned peptides in mice immunized with anti-CD91 antibodies (see Fig. 3B at page 6131) and successfully inhibit gp96-CD91 interactions in mice challenged with Meth A fibrosarcoma (see page 6133, column 1, Fig. 5 caption and page 6131,column 2, 2nd full paragraph). Thus, by modulating the interaction of an α2MR with gp96-chaperoned peptides the anti-α2MR antibodies blocked the ability of gp96-chaperoned peptides to induce an immune response and thereby modulated an immune response *in vivo* allowing Meth A fibrosarcoma to grow. Similarly, Binder *et al.* (2002, Cancer Immunity 2:16-24, submitted herewith as IDS reference No. C03) showed successful inhibition of gp96-CD91 interactions, as evidenced by growth of B16-F10-OVA tumors in mice immunized with anti-CD91 antibodies (see page 19, indicated as 4 of 9). Thus, Applicants assert that the *in vitro* results obtained in live cell-based assays described in the specification can be extrapolated to *in vivo* results without engaging in undue experimentation and therefore the claimed methods are fully enabled with respect to modulating an immune response both *in vitro* and *in vivo*.

Results obtained by Basu *et al.* (2001, Immunity 14:303-313, submitted herewith as IDS reference No. C04) demonstrate the ability of anti-α2MR antibodies to interfere with the interaction of various types of HSPs (*i.e.*, gp96, hsp70, and hsp90) with the α2MR and modulate HSP mediated antigen representation in representation competent cells, *i.e.*, RAW264.7 (see page 309, Fig. 5C caption). The specification describes similar results using immune sera to the 80 kDa fragment of the α2MR and gp96 labeled with FITC in RAW264.7 cells (see page 71, lines 14-20 and page 72, line 29 through page 73, line 12). Thus, as taught in the specification, anti-α2MR antibodies can be used to modulate the interaction of various HSPs with the α2MR.

The above references indicate that the *in vitro* antibody data presented in the specification is predictive of *in vivo* modulation of an immune response.

With respect to α2MR fragments that interfere with the interaction of an HSP and α2MR to modulate an immune response, the specification teaches examples including α2MR fragments, *e.g.*, the 80 kDa fragment, that bind α2MR ligands as described above in response to the written description rejection. The 80 kDa fragment was found to bind the heat shock protein gp96 in two different re-presentation competent cell types *in vitro* (see page 72, lines 13-28). This experimental data presented in the specification demonstrates that an α2MR-ligand binding peptide can modulate the interaction of an HSP and α2MR by competitive binding to the HSP in cell types capable of modulating an immune response via re-presentation of HSP chaperoned peptides *in vivo*. There is no reasonable basis to believe that a fragment of α2MR with ligand-binding properties, *i.e.*, having an HSP-interacting portion of α2MR described in the specification, could not successfully be used *in vivo* to modulate the interaction of an HSP and the α2MR to modulate an immune response. Moreover, the specification also teaches assays that can be used to identify α2MR fragments that can be used in the methods of the invention (see page 40, line 16 through page 41, line 3 and Section 5.2.2). In view of the teachings and example presented in the specification, one skilled in the art would be able to identify α2MR fragments that are capable of interfering with the interaction of an HSP and the α2MR without engaging in undue experimentation.

With respect to an α2M fragments and HSP fragments, the specification teaches use of such fragments which are capable of binding α2MR (see page 41, lines 5 and 6, and page 42, lines 11-13). The specification also teaches *in vivo* assays that can be used to identify HSP fragments and α2M fragments that can be used in the methods of the invention (see page 41, lines 13-14 and Section 5.2.2). Moreover, the experimental data presented in the specification demonstrates that α2M inhibits re-presentation of gp96-chaperoned peptides

in vitro (see page 73, lines 20-29). In addition, Binder and Srivastava showed that α2M inhibited re-presentation of gp96-chaperoned peptides in mice immunized with α2M demonstrating that α2M can interfere with the interaction of an HSP and the α2MR to modulate an immune response *in vivo* (see Fig. 3B caption at page 6131, column 1).

The α2M assays described in the specification combined with the disclosure regarding α2M fragments and HSP fragments enable one skilled in the art to identify α2M fragments and HSP fragments that can be used in the methods of the invention to modulate the interaction of an HSP and the α2MR or inhibit an immune response. Thus, in view of the teachings of α2M fragments, HSP fragments, and α2MR fragments in the specification, the exemplary structural and functional correlations for modulating the interaction of an HSP and α2MR, and the confirmation that assays, such as those taught in the specification, are predictive of modulation of an immune response *in vivo*, one skilled in the art would be able to use α2M fragments, HSP fragments, and α2MR fragments to modulate an immune response without undue experimentation.

In view of the *in vitro* experimental data demonstrated in the specification and the correlation between *in vitro* and *in vivo* data shown in the references cited herein, following the teachings of the specification, one skilled in the art would be able to identify and use an antibody, α2M fragments, HSP fragments, and α2MR fragments to successfully interfere with the interaction of an HSP and the α2MR or bind the α2MR and thereby modulate an immune response *in vivo*.

The Examiner contends that the treatment of cancer is unpredictable, including extrapolating from *in vitro* to *in vivo* protocols in the absence of critical working examples. Applicants respectfully point out that claims 31 and 71 do not require treatment of cancer, nor does claim 88, which merely specifies that the immune response is to a cancer antigen. Thus, the question of whether treatment of cancer is enabled is irrelevant to the instantly claimed invention.

With respect to modulation of an immune response to a cancer, in accordance with case law, *in vitro* data is sufficient as long as it is reasonably correlated with a pharmacologically useful *in vivo* response. Moreover, both Binder and Srivastava and Binder *et al.* demonstrate *in vivo* modulation of tumor growth using the methods of the invention as described above. Thus, the *in vitro* data combined with the teachings of the specification provide sufficient enabling disclosure to enable one skilled in the art to practice the methods of the invention to successfully modulate an immune response to a cancer *in vivo*.

In view of the forgoing arguments and amendments, applicants respectfully

request the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

3. THE REJECTION UNDER 35 U.S.C. § 102 (e), AS BEING ANTICIPATED BY NUIJENS *ET AL.*

Claims 31, 71, 76, and 80-91 have been rejected under 35 U.S.C. § 102 (e) as allegedly anticipated by Nuijens *et al.* (U.S. Patent No. 6,333,311, hereafter "Nuijens"). The Examiner points out that Nuijens teaches the administration of lactoferrin for the modulation of an immune response and that because lactoferrin is a ligand of the α2MR it would inherently interfere with the binding of HSP to the α2MR.

Claims 31 and 71 have been amended to claims 31 and 71 have been amended to indicate that "a purified compound" is "selected from the group consisting of an antibody, an alpha (2) macroglobulin fragment, an alpha (2) macroglobulin receptor fragment, and a heat shock protein fragment" and "selected from the group consisting of an antibody, an alpha (2) macroglobulin fragment, and a heat shock protein fragment," respectively.

Applicants submit that the rejection has been overcome by the amendment to the claims and respectfully request the Examiner's withdrawal of the rejection under 35 U.S.C. § 102(e), over Nuijens.

4. THE REJECTION UNDER 35 U.S.C. § 102 (b), AS BEING ANTICIPATED BY HYMAN *ET AL.*

Claims 31, 71, 76, 78, 80-85, and 91-93 have been rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by International Publication No. WO 97/04794, referred to by the Examiner as Hyman BT *et al.* [sic, Strickland *et al.*], hereafter "Hyman." The Examiner contends that the agents, including antibodies and peptides, disclosed by Hyman would inherently modulate an immune response because the agents would block the binding of HSPs to the α2MR.

Applicants respectfully submit that this assertion does not provide the requisite rationale or evidence of inherency. In order for a prior art reference to amount to an inherent anticipation of a claim, all the elements of the claim must necessarily, inevitably and always result from the prior art disclosure; mere possibilities or probabilities are not sufficient. *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (citing *Hansgirg v. Kemmer*, 102 F.2d 212, 214, 40 U.S.P.Q. 665, 667 (C.C.P.A. 1939). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. *Id.* Substantial uncertainty regarding the existence of a product in the prior art, *i.e.*, uncertainty as to whether the inherent characteristic *necessarily* flows from the teaching of the prior art reference, is

enough to preclude anticipation. *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983; *Bristol-Myers Co. v. USITC*, 15 U.S.P.Q.2d 1258 (Fed. Cir. 1989). Moreover, the Manual of Patent Examination Procedure ("MPEP") states:

> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).
>
> See MPEP § 2112.

In the present instance, the evidence discussed below indicates that the agents disclosed by Hyman would not likely interfere with the interaction of an HSP and α2MR, and therefore would not modulate the immune response. The agents of Hyman which recognize α2MR (also known as LRP) bind to the amyloid precursor protein ("APP") binding site on α2MR (called group I agents by Hyman) (see page 4, lines 17-19). These agents would not be expected to block the binding of HSPs to the α2MR, because APP and HSPs bind to different sites of the α2MR extracellular domain.

The specification demonstrates that HSPs bind to an 80 kDa fragment of the α2MR, which corresponds to a portion of cluster I (which is extracellular) of α2MR (confirmed in two independent assays as disclosed at page 71, line 34 through page 72, line 28 and Fig. 8b which shows the full length amino acid sequence of the α2MR with the location of the 80 kDa fragment highlighted in bold).

Hyman describes the use of an anti-LRP antibody (*i.e.*, an anti- α2MR antibody) for use in treating Alzheimer's disease (see page 23, lines 4-19 and page 8, lines 27-31. This antibody blocks the interaction of amyloid precursor protein (APP) with the α2MR. Such an antibody would not be expected to interfere with the interaction of an HSP to the α2MR because APP and HSPs interact with the receptor in fundamentally different ways and at different portions of the α2MR.

There are two known ways in which APP interacts with the α2MR. Firstly, APP interacts with the α2MR through its interaction with a scaffolding protein. Applicants invite the Examiner's attention to Herz and Strickland (2001, J. Clin. Invest. 108:779-784, submitted herewith as IDS reference No. C05, hereafter "Herz and Strickland"). APP is shown to interact with an intracellular portion of the α2MR via a cytoplasmic scaffolding protein (see Fig. 2 (center), page 781). Since the HSP-binding portion of α2MR is extracellular, it is clear that HSPs are interacting with α2MR via a different portion of the

α2MR molecule than APP.

Secondly, Applicants invite the Examiner's attention to Goto and Tanzi (2002, J. Mol. Neurosci. 19:37-41, submitted herewith as IDS reference No. C06) which demonstrates that APP binds to an extracellular portion of the α2MR located in cluster II of the α2MR (see abstract). Thus, HSPs bind cluster I, while APP binds cluster II of the α2MR.

The forgoing indicates that the anti-α2MR antibody of Hyman would be unlikely to modulate the interaction of an HSP and the α2MR, since the interactions are at different places on the α2MR. Thus, a finding of inherent anticipation is improper.

With respect to claim 93 drawn to antibody fragments, Applicants point out that Hyman discloses using antibody fragments that bind to the APP binding site on α2MR. For the same reasons as described above with respect to whole antibodies, the antibody fragments of claim 93 are not inherently anticipated by the disclosure of Hyman[1].

In view of the amendments and remarks above, Hyman does not disclose the claimed methods of the instant invention either explicitly or inherently. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C.§ 102(b) should be withdrawn.

[1] With respect to the Examiner's statement implying that Alzheimer's disease is a dense deposit disease, Applicants respectfully disagree. The skilled artisan would clearly understand dense deposit disease, as used in the specification, to mean an autoimmune disease, for example, a kidney disease caused by deposits in the basement membranes of the kidneys. According to the art-recognized reference, The Merck Manual of Diagnosis and Therapy, dense deposit disease is type II membranoproliferative glomerulonephritis, an immune-mediated disorder characterized by chronic immune complex deposition in the glomeruli of the kidneys (see, The Merck Manual of Diagnosis and Therapy, 1999, Beers and Berkow eds., Merck Research Laboratories, Whitehouse Station N.J., pp. 1871 and 1872, submitted herewith as IDS reference No. C07).

CONCLUSION

Entry of the foregoing amendment and remarks into the record of the above-identified application is respectfully requested. Applicants submit that the remarks and amendments made herein now place the claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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